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Статья

Synthesis and Singlet Oxygen Generation Study of 13(1)−N−Piperazinyl Chlorin e_6 15(2),17(3)−Dimethyl Ester

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A new monoamide derivative of chlorin e_6 containing the piperazine fragment was synthesized and identified with MALDI MS, ^1H NMR, UV-Vis and fluorescence spectroscopy. Our photophysical data $\{\lambda^I_{max}(lg\varepsilon) = 665\ (4.62);\ \gamma_\Delta = 0.52\pm0.06\}$ indicate that this macrocycle may be considered as a promising sensitizer for photodynamic therapy.

Keywords: Chlorophyll, photosensitizers, piperazine, synthesis, photophysics, singlet oxygen.

Синтез и исследование генерации синглетного кислорода 15(2),17(3)−диметиловым эфиром 13(1)−N−пиперазинилхлорина e_6

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Впервые синтезировано и спектрально идентифицировано посредством МАЛДИ масс-спектрометрии, ^1H ЯМР, флуоресцентной и электронной спектроскопии поглощения новое моноамидное производное хлорина e_6, содержащее пиперазиновый фрагмент. Фотофизические исследования $\{\lambda^I_{max}(lg\varepsilon) = 665\ (4.62);\ \gamma_\Delta = 0.52\pm0.06\}$ показали, что соединение может рассматриваться в качестве сенсибилизатора для фотодинамической терапии.

Ключевые слова: Хлорофилл, фотосенсибилизаторы, пиперазин, синтез, фотофизика, синглетный кислород.

Introduction

Chlorophyll (Chl) derivatives as well as other natural and synthetic pigments are being intensively studied for last several decades as new materials for nanotechnology and medicine.[1] In particular, they are proven to be effective second generation photosensitizers (PC) for photodynamic therapy (PDT).[2-10] Taking into account numerous requirements for

the medical utilization of PC, the chemical modification of the chlorophyll molecule should provide at least sufficient solubility in an aqueous-rich medium and simultaneously effective penetration through cell membranes.[2-6] The main reaction centers of Chl series are vinyl and ester groups, carbonyl function and the cyclopentanone ring.[11,12] The disclosure of the latter through weak organic bases leads to a number of chlorin e_6 derivatives.[12] Chlorin e_6 and its

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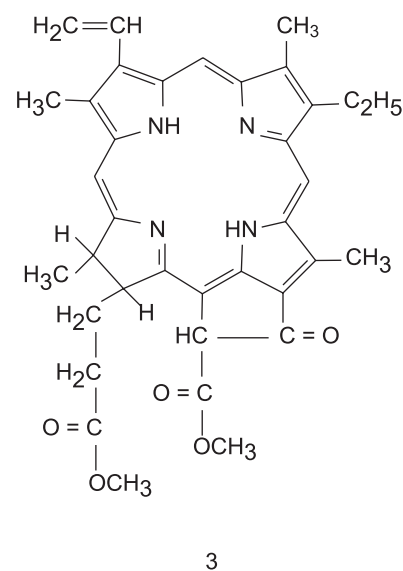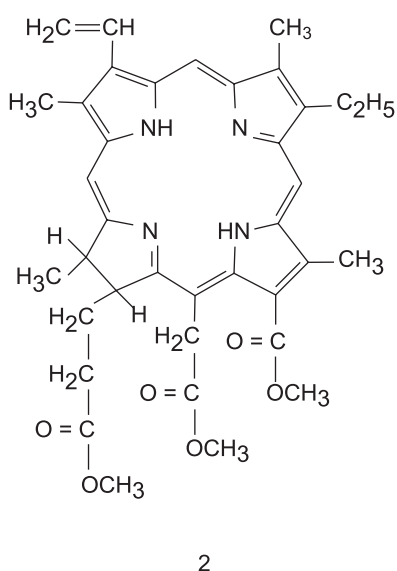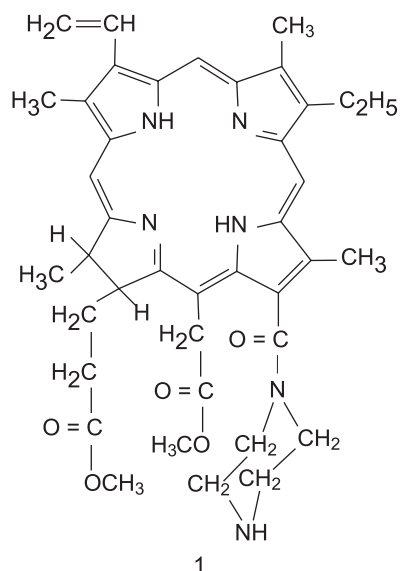
esters are found to be a good PC revealing low dark toxicity, high yield of singlet oxygen generation and sufficient hydrophobicity/hydrophilicity balance.[3-6] The main goal of many recent studies is to obtain new hybrid materials on the chlorin e_6 platform to achieve a double or even triple action in one drug to create the so called theranostics.[6] Thus, in this work we present the results of our efforts devoted to synthesis and the spectroscopic study of a new chlorin e_6 derivative containing a fragment of piperazine (Pz), which is a structural component of a number of antispasmodic, vermicidal and antitumor drugs.[13] It is reasonable to expect that double photodynamic and possible antimicrobial action of this conjugate (13(1)-*N*-piperazinyl chlorin e_6 15(2),17(3)-dimethyl ester, **1**), which is structurally similar to famous PC based on the chlorin e_6 trimethyl ester platform (**2**), may be useful for clinical application at PDT.[7,10]

Experimental

13(1)-N-Piperazinyl chlorin e_6 15(2),17(3)-dimethyl ester (1). Methylpheophorbide *a* (100 mg, 0.165 mmol) **3** was dissolved in 25 ml of benzene and was added to a solution of piperazine (0.545 g, 6.34 mmol) in the same solvent. The reaction mixture was stirred for 2 hours at room temperature, diluted with chloroform, washed consequently with water, dilute HCl solution and water again to reach neutral p*H*. The solvent was evaporated, and the reaction mixture was subjected to silica gel column chromatography using chloroform and chloroform-methanol mixtures (10 vol. % of MeOH) as an eluent. For more accurate product purification it was exposed to repeated chromatography. Yield of the amide **1** obtained as a dark green crystals is 12.4 mg (10.85 %). Mass spectrum (MALDI) *m/z* (%): 693 (100) [M]+, 716 (23) [M+Na]+. ^{1}H NMR (500 MHz, CDCl$_3$, 25 °C) δ_H ppm: *Major isomer*: 9.74 (1H, s, H[10]), 9.70 (1H, s, H[5]), 8.87 (1H, s, H[20]), 8.15 (1H, dd, *J*=18.1 and 11.5 Hz, H[3(1)]), 6.39 (1H, br. dd, *J*=17.9 and 4.5 Hz, H[3(2) (trans)]), 6.17 (1H, br. dd, *J*=11.4 and 3.5 Hz, H[3(2) (cis)]), 5.82 and 5.10 (1H each, both d, *J*=19.2 and 19.4 Hz, 15-C*H*$_2$CO$_2$CH$_3$), {13-CONC$_4$H$_8$NH: 4.72 (1H, br. dt, *J*=13.0 and 3.8 Hz), 4.05–4.00 (1H, m), 3.25–3.11 (2H, m), 3.06–2.90 (1H, m), 2.37–2.14 m (4H, incl. 2.20 (1H, s, 13-CONC$_4$H$_8$N*H*)}, 4.50 (1H, q, *J*=7.3 Hz, H[18]), 4.43 (1H, br. d, *J*=8.2 Hz, H[17]), 3.88 (3H, s, 15-CH$_2$CO$_2$C*H*$_3$), 3.67 (3H, s, 17-CH$_2$CH$_2$CO$_2$C*H*$_3$), 3.59 (3H, s, 12-C*H*$_3$), 3.54 (3H, s, 2-C*H*$_3$),

3.36 (3H, s, 7-C*H*$_3$), 3.85–3.81 (2H, m, 8-C*H*$_2$CH$_3$), 2.77–2.54 (4H, m, 17-C*H*$_2$C*H*$_2$CO$_2$CH$_3$), 1.79–1.73 (6H, m, 18-C*H*$_3$; 8-CH$_2$C*H*$_3$), -1.67 (br. s, [21]NH), -1.87 (br. s, [23]NH); *Minor isomer*: 9.71 (1H, s, H[10]), 9.67 (1H, s, H[5]), 8.82 (1H, s, H[20]), 8.11 (1H, dd, *J*=18.3 and 11.3 Hz, H[3(1)]), 6.39 (1H, br. dd, *J*=17.9 and 4.5 Hz, H[3(2) (trans)]), 6.17 (1H, br. dd H[3(2) (cis)], *J*=11.4 and 3.5 Hz), 5.46 and 5.26 (1H each, both d, *J*=19.1 and 19.2 Hz, 15-C*H*$_2$CO$_2$CH$_3$), {13-CONC$_4$H$_8$NH: 4.41–4.34 (1H, m), 4.05–4.00 (1H, m), 3.25–3.11 (2H, m), 3.06–2.90 (1H, m), 2.37–2.14 (4H, m incl. 2.20 (1H, s, 13-CONC$_4$H$_8$N*H*)}, 4.50 (1H, q, *J*=7.3 Hz, H[18]), 4.43 (1H, br. d, *J*=8.2 Hz, H[17]), 3.83 (3H, s, 15-CH$_2$CO$_2$C*H*$_3$), 3.64 (3H, s, 17-CH$_2$CH$_2$CO$_2$C*H*$_3$), 3.55 (3H, s, 12-C*H*$_3$), 3.52 (3H, s, 2-C*H*$_3$), 3.35 (3H, s, 7-C*H*$_3$), 3.85–3.81 (2H, m, 8-C*H*$_2$CH$_3$), 2.77–2.54 (4H, m, 17-C*H*$_2$C*H*$_2$CO$_2$CH$_3$), 1.79–1.73 (3H, m, 8-CH$_2$C*H*$_3$), 1.68 (3H, d, *J*=7.2 Hz, 18-C*H*$_3$), -1.57 (br. s, [21]NH), -1.72 (br s, [23]NH).

Mass spectra were recorded on the MALDI FAB MS-spectrometer Shimadzu AXIMA Confidence using 2,6-dihydroxybenzoic acid as a matrix. ^{1}H NMR spectra were registered in CDCl$_3$ on the spectrometer Bruker Avance 500 (500 MHz). Absorption and fluorescent spectral measurements were performed at 298 K with D8 spectrophotometer (Drawell, China) and CM 2203 specrofluorimeter (Solar, Belarus').

Methylpheophorbide a (3). Mass spectrum (MALDI) *m/z* (%): 607 (100) [M]+. ^{1}H NMR (500 MHz, CDCl$_3$, 25 °C) δ_H ppm: 9.55 (1H, s, H[10]), 9.42 (1H, s, H[5]), 8.59 (1H, s, H[20]), 8.02 (1H, dd, *J*=17.8 and 6.4 Hz, H[13(1)]), 6.28 (1H, s, H[13(2)]), 6.26 (2H, br. dd, *J*=17.9 and 11.6 Hz, H[3(2) (trans) and (cis)]), 4.50–4.20 (2H, m, H[17], H[18]), 3.90 (3H, s, 15-CHCO$_2$C*H*$_3$), 3.72 (2H, q, *J*=7.9 Hz, 8-C*H*$_2$CH$_3$), 3.71 (3H, s, 17-CH$_2$CH$_2$CO$_2$C*H*$_3$), 3.60 (3H, s, 12-C*H*$_3$), 3.43 (3H, s, 2-C*H*$_3$), 3.27 (3H, s, 7-C*H*$_3$), 2.65–2.17 (4H, m, 17-C*H*$_2$C*H*$_2$CO$_2$CH$_3$), 1.83 (3H, d, *J*=7.4 Hz, 18-C*H*$_3$), 1.72 (3H, t, *J*=15.1 and 7.6 Hz, 8-CH$_2$C*H*$_3$) 0.58 (br. s, [21]NH), -1.59 (br. s, [23]NH). Methylpheophorbide *a* was prepared from Spirulina Platensis (China) according to well known procedure.[12,14] Anhydrous 98 % piperazine (Panreac) was used without further purification. Solvents (benzene, chloroform, methanol, DMF, 1-octanol) were purified according to described procedure.[15]

The singlet oxygen photoformation was chemically proved by means of the tetracene oxidation under exposure of its solution in the presence of **1** with an initial concentration of 1·10^{-5} mol/l to light passing through KS-11 glass bandpass filter with a short-wave transmission cut of at 580 nm. A solution was irradiated in a glass cell. The oxidation of tetracene with an initial concentration of 7·10^{-5} mol/l was monitored spectrophotometrically in the region from 400 to 500 nm. The irradiation of tetracene in 1-octanol caused

changes in the intensity of its observed bands at 443 and 473 nm. According to the results published in [16], these changes are due to tetracene oxidation by $^1O_2$.

The time resolved photoluminescence of $^1O_2$ measurements were taken on an LIF-200 pulsed laser fluorimeter with 337 nm nitrogen laser with pulses of 20 μJ, 2 ns pulse duration and 30 Hz pulse repetition frequency. The $^1O_2$ luminescence was measured with FD-10 GA germanium detector through an IKS glass bandpass filter with a short-wave transmission cut of at 980 nm. Detailed description of the equipment was given elsewhere.[17]

Results and Discussion

Synthesis and Spectral Identification

Amidation of 13(1) position in chlorin e_6 molecule passes through opening cyclopentanone ring of methylpheophorbide a **3** molecule. The scheme of this reaction mechanism proceeds as a nucleophilic substitution at 13(1) carbon atom of the molecule **3** and includes stages of the addition of the nucleophile reagent to the double bond of carbonyl group, cleavage of the C-C-bond of the cyclopentanone ring of the macrocycle to form stable conjugated carbanion at 15(1)-position and excessive proton

Figure 1. Normalized UV-Vis and fluorescence spectra of compound **1** in 1-octanol.

migration from N- to C-center.[12]

Absorption spectrum of piperazinyl derivative **1** of chlorin e_6 is typical for such chlorophyll-like species.[18,19] It contains the intensive Q_x-band at 665 nm and the Soret band at 401 nm arising from the π-π*-electron transfer (Figure 1, Table 1). The solvatochromic effect for this compound is negligible; absorption maxima are nearly the same in DMF and 1-octanol, respectively. All bands in absorption spectra of the initial compound **3** are shifted bathochromically for about 10 nm for the Soret band and for 3–4 nm for the Q-band (see Table 1). It is necessary to note that the changes in absorption spectra of different chlorins do not usually exceed 1–2 nm. For instance, spectra of compounds **1** and **2** are nearly identical.[19]

The synthesized **1** reveals the extended red fluorescence with a single spectral band at 670 nm which is nearby to 676 nm observed for methylpheophorbide a **3** (Figure 1, Table 1). The position of the maxima in fluorescence spectra does not depend on the nature of the solvent used. The Stocks's shift (Δv_1^{St}) calculated for **1** from absorption and emission spectral data does not exceed the value for chlorin e_6 in ethanol (5–6 nm) given.[20] This quantity is similar for aromatic tetrapyrroles with a relatively planar structure.[21] Shifts for the starting macrocycle **3** are 1–3 nm higher.

All protons in ^{1}H NMR spectra of chlorin molecule **1** are assigned according to the numerous data published for closely related macrocycles.[11,12] The typical changes of spectra ^{1}H NMR on going from methylpheophorbide a **3** to chlorin e_6 derivative **1** are in the disappearance of singlet of 13(2)-CH proton at 6.28 ppm and the increase of doublets in the downfield region between 5 and 6 ppm (Figure 2). This behavior results from the spin-spin interaction of two magnetically non-equivalent 15(1)-CH$_2$ protons. One more important feature of proton NMR of chlorin e_6 amide is the appearance of the signal at about 2.2 ppm corresponding to piperazine NH-proton. The synthesized sensitizer **1** likewise other similar chlorin e_6 amides[12] gives two sets of signals in ^{1}H NMR spectra. This feature is common for all known tertiary 13(1)-substituted amides of chlorin e_6. It is explained by the existence of two stable atropisomers (major and minor isomers) of such compounds both in a solution and a solid state.[12,22] The presence of double set of signals complicates spectra NMR essentially (Figure 2). However, piperazinyl substitution can be easily proven by the appearance of new
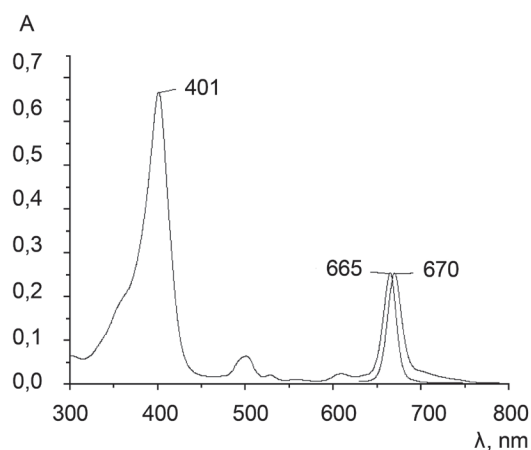
Table 1. Photophysical characteristics of chlorophyll derivatives in organic solvents (C=7·10^{-6} mol·l^{-1}).

Comp.	Solvent	Absorption spectra, λ(lgε)					Emission spectra		Singlet oxygen generation	
		Soret	IV	III	II	I	λ_1	Δv_1^{St}, nm	γ_Δ	τ, μs
1	1-Octanol	401 (5.01)	501 (4.00)	529 (3.52)	609 (3.57)	665 (4.59)	670	5	0.52±0.06	19±1
1	DMF	401 (5.17)	501 (4.11)	529 (3.50)	608 (3.64)	664 (4.70)	670	6	–	–
3	1-Octanol	412 (4.73)	507 (3.80)	538 (3.77)	611 (3.71)	669 (4.44)	676	7	0.47±0.05	18±1
3	DMF	412 (5.08)	507 (4.10)	537 (4.05)	609 (3.97)	667 (4.71)	676	9	–	–

signals between 2.1 and 4.7 ppm, equivalent to 9 protons, some of them are essentially shielded by a ring current of the aromatic chlorin macrocycle. This substitution occurs namely at position 13 of chlorin macrocycle as far as the number of signals of methyl groups within 3–4 ppm for the compounds **1** and **3** remains constant.

Singlet Oxygen Generation and its Photostability

Macrocycle **1** is believed to be the typical photosensitizer of $^1O_2$ ($^1\Delta_g$). We have studied its photogeneration of singlet oxygen both with the acceptor method and also by measuring photoluminescence at ~1270 nm. Measurements were fulfilled in 1-octanol medium modelling human cell membranes.[23]

The decay kinetic of photoluminescence in octanol solution is biexponential with a long-lived component. Its lifetime is found to be equal to 19±1 µs. This value is in good agreement with the $^1O_2$ lifetime determined by Rodgers,[24] and it is also nearly identical to some other organic solvents in absence of any singlet oxygen quenchers.[25]

The $^1O_2$ quantum yield (γ_Δ) has been determined by comparing the initial intensities of $^1O_2$ luminescence in solutions of compound **1** and palladium mesoporphyrin IX dimethyl ester (PdMP) at A_{337}=0.77. The γ_Δ value for PdMP equals to 1.[26] The initial intensities have been obtained from the decay curve of $^1O_2$ luminescence by a standard technique implying an exponential dependence. This method gives γ_Δ=0.52±0.06 for **1** in 1-octanol. The γ_Δ value for more hydrophilic compound **1** is found to be 0.47±0.05 in the same solvent. Nevertheless, it is higher than γ_Δ for some synthetic chlorins widely used as commercial PC. For instance, the $^1O_2$ quantum yield for Foscan (5,10,15,20-tetrakis-*m*-hydroxyphenylchlorin) is 0.43 in ethanol.[2]

As it has been mentioned above (see Experimental), the changes observed in absorption spectra of the tetracene added arise from its oxidation by $^1O_2$. In fact, the sensitizer bleaching in 1-octanol does not occur in the absence of tetracene under the same experimental conditions. The detailed analysis shows that this process is very slow. The first-order bleaching of both compounds gives effective rate constants. The ratio of these constants is equal to $4.4 \cdot 10^2$, which is almost identical to that for the true rate constants of both oxidation reactions by $^1O_2$.[27] Assuming that the true rate constant of tetracene oxidation is $8 \cdot 10^6$ l·mol^{-1}s^{-1} in ethanol,[27] the value of $1.8 \cdot 10^4$ l·mol^{-1}s^{-1} for the true rate constant for **1** can be evaluated.

This means that **1** is more stable for the photobleaching in comparison with other known tetrapyrrolic PC presented in [2]. Unfortunately, in the presence of tetracene the oxidation rate strongly increases due to the influence of tetracene peroxide products causing **1** oxidation.

Conclusions

Thus, we have synthesized 13(1)-*N*-piperazinyl chlorin e_6 15(2),17(3)-dimethyl ester **1** from methylpheophorbide *a* **3** for the first time using the amidation reaction. The obtained product has been identified with MALDI MS, ^{1}H NMR, UV-Vis and fluorescence spectroscopy. Macrocycle **1** shows photophysical properties that are typical for the photosensitizers generating singlet oxygen $^1O_2$ ($^1\Delta_g$) species. It shows intensive absorption in a red region of UV-Vis spectra, a high quantum yield of singlet oxygen and moderate photobleaching in the presence of $^1O_2$ species.
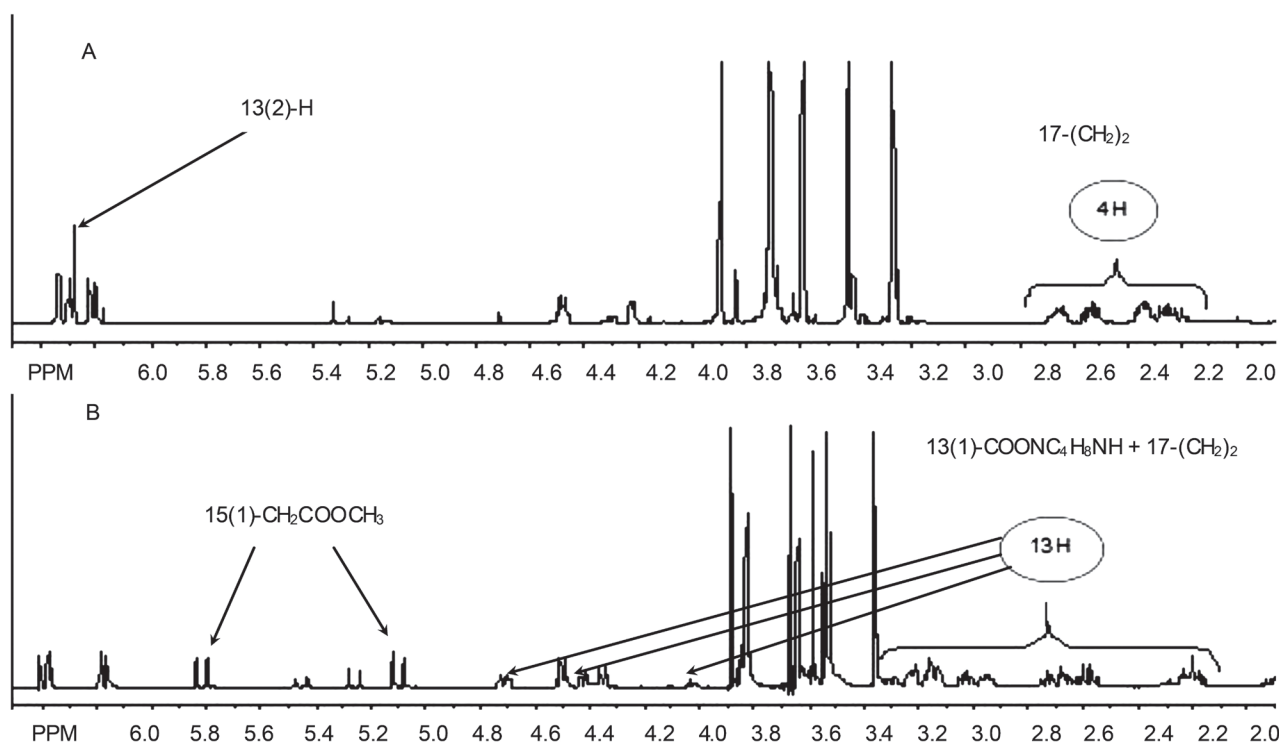

Figure 2. ^{1}H NMR data for compounds **3** (A) and **1** (B) measured in CDCl$_3$.

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